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10/617,915	07/10/2003	Jerome James Workman JR.	MLA.026CP	4223

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EXAMINER	
SCHUBERG, LAURA J	

ART UNIT	PAPER NUMBER
1657	

NOTIFICATION DATE	DELIVERY MODE
07/29/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/617,915	WORKMAN ET AL.	
	Examiner	Art Unit	
	Laura Schuberg	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19,23-36,38-42 and 54-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,23-36,38-42 and 54-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/30/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is responsive to papers filed 04/30/2009. Claims 19 and 33 have been amended. No claims have been newly added or newly canceled.

Claims 19, 23-36, 38-42, 54-56 are pending and have been examined on the merits.

Previous Rejections

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 19, 23-26, 28, 29, 30-36, 38, 39, 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chick et al (US 6,040,194) in view of Cote et al (US 6,485,703 B1), Walt et al (US 6,377,721 B1) and newly added Van Antwerp et al (US 6,319,540-from IDS).

Amended claims 19 and 33 are drawn to methods of monitoring the concentration of one or more analytes or *in vivo* blood glucose levels respectively. The methods comprise applying a skin sensor composition to a surface of the skin for a predetermined period of time, wherein the composition comprises a reporter dye and a marker dye, wherein the wavelength and/or intensity of fluorescence emission or absorbance of the reporter dye varies in proportion to a change in concentration of a metabolite or analyte, and the wavelength and/or intensity of fluorescence emission or absorbance of the marker dye does not vary in proportion to a change in the concentration of the metabolic or analyte and further wherein the marker dye comprises coumarin; causing penetration of the composition to a depth of about 10 μm, wherein said depth corresponds with the bottom of the dead stratum corneum layer, to about

175 µm, wherein said depth corresponds with the top of the dermal layer, into the epidermis; and monitoring a change in **intracellular** concentration of metabolites or analytes (glucose) by detecting changes in fluorescence emission or absorbance of the reporter dyes using an optical reader, and correlating the change in **intracellular** concentration of the metabolites or analytes (glucose) with in vivo blood concentration of the metabolite or analyte (in vivo blood glucose levels). Dependent claims are drawn to the type of stain or dye used, the type of transport technique used, and the minimum wavelength detected being above 450 nm.

Claims 30 and 40 are drawn to the methods of claims 19 and 33 respectively and includes the additional limitations wherein the penetration depth into the epidermis is accomplished by combining the composition with molecular size attachments.

Applicant defines "molecular size attachments" as adducts to the fluorescent moieties of SMMRs to include, but are not limited to structural modifications of fluorescent SMMRs as the additions to the fluorescence structure of: acetoxy methyl esters and several others (page 14 para 167).

Claims 31 and 41 are dependent on claims 19 and 33 respectively and include the additional limitations of the predetermined time period that the skin sensor composition is applied for.

The limitation of the depth in the skin of 10 µm to 175 µm is interpreted to mean the epidermal layer of the skin. In addition, this limitation is interpreted as not excluding the dermal layer of the skin as long as the composition passes through the epidermis first.

The new limitation of the "marker dye" is interpreted as being equivalent to a reference or calibration dye.

Chick teaches an *in vivo* method and sensor for detecting an analyte in an individual qualitatively or quantitatively. The sensor is placed in communication with the bodily fluids and once in place the sensor does not exit the skin of the individual. Once the sensor is in place, it is illuminated with radiation transdermally and the fluorescence reagent associated with the presence of the analyte is measured (column 2 lines 31-50). For *in vivo* use, the reagents comprising the fluorescence reagent are placed in, on, or under the skin in communication with (e.g. contacting) body fluid containing the analyte of interest (column 16 lines 24-28). This is interpreted to include the epidermis, thus meeting the limitation for depth in skin of the sensor (claim 19). Wherein glucose is the analyte detected is taught (column 6 lines 35-38) as well as wherein the dye is combined with glucose oxidase and uses an oxidative metabolic pathway to measure glucose levels (column 15 lines 35-47) (claims 33 and 24). BCECF is specifically taught as a suitable pH probe (column 14 line 63), which also meets the limitations for a xanthene dye (as identified by Applicant page 8 para 90 of the specification) (claims 23,25,26,34-36). A variety of modes of placing the reactants in communication with the analyte are taught including tattooing and a transcutaneous patch (column 17 lines 6-12) (claims 29 and 39). This would inherently include formulations such as a solvent or a disposable gel film patch as well as wicking (from the patch) as a form of transport for penetration of the skin (claims 28, 29, 38 and 39). In addition, spectra were collected by exciting fluorescein at 472 nm and scanning the emission from 500-650 nm (column 11

lines 39-41) (claims 32 and 42). Comparison of fluorescence and wavelength to that found in the absence of the analyte is also taught as well as correlating the change in fluorescence intensity, emission spectrum, excitation spectrum, or excited state lifetime of the fluorescence reagent with the presence or amount of analyte in the individual (column 18 lines 5-27).

Chick is silent with regard to intracellular or extracellular concentrations of analytes measured and does not specifically indicate the time period of application. Chick teaches BCECF, but does not specifically teach the use of BCECF with a molecular size attachment. Chick also does not teach the use of a marker dye.

Cote teaches compositions and methods for analyte detection (abstract). Cote teaches the importance of monitoring both intra- and extra-cellular analytes, particularly intracellular glucose in diabetic patients since the acute problems related to diabetes are correlated to intracellular glucose levels. Too much insulin causes low glucose in both extracellular and intracellular fluid (insulin shock). Too little insulin, or insulin receptor resistance, causes low glucose intracellularly and high glucose extracellularly. Information may be gained simultaneously by using two particle sizes: one that is small enough for phagocytosis and one that is too large for phagocytosis (column 24 lines 30-67). Intracellular glucose levels may vary more relative to plasma glucose concentrations in diabetics. Detection of low intracellular glucose levels may aid in monitoring changes in glucose in diabetes or the effectiveness of medications (column 13 lines 24-30).

Walt teaches that the acetoxymethyl (AM) ester form of BCECF (an intracellular dye) is non-fluorescent in solution, cell membrane permeant and passively enters the cell where, once inside the cell, the lipophilic blocking groups are cleaved by non-specific esterases resulting in an increase in fluorescent intensity. This increase in fluorescent intensity is indicative of the cell viability as a pH indicator (column 16 lines 48-61).

Van Antwerp et al teach the use of a calibration fluorophore (fluorescent dye) in combination with an amplification dye (reporter dye) for the detection of *in vivo* analytes (such as glucose). This combination of dyes is taught to eliminate errors due to registration and variations of light transport through the skin (e. g, caused by different skin tones) (column 16 lines 24-30). The calibration fluorophore provides a signal not interfering with the signal from the amplification components and includes fluorescent dyes such as coumarin to be used during the *in vivo* detection of analytes such as glucose (column 17 lines 4-26).

Therefore, it would have been obvious for one of ordinary skill in the art to include monitoring of intracellular concentrations of one or more metabolites in the method of Chick and correlating them with blood glucose levels because Cote teaches the importance of monitoring both intra- and extra-cellular analytes, particularly intracellular glucose in diabetic patients since the acute problems related to diabetes are correlated to intracellular glucose levels. Cote points out that the relationship between intracellular and extracellular levels can be significant for patient care and diagnosis and extracellular glucose-sensing particles would give levels very similar or

identical to blood glucose (column 24 lines 46-65). One of ordinary skill in the art would have had a reasonable expectation of success because Cote teaches that there are known methods for monitoring intracellular concentration such as those that use different size particles (column 24 lines 62-65) and Chick also teaches that selectivity can be accomplished using molecular size (column 16 line 47). In addition, Walt teaches that there are fluorescent dyes (such as acetoxymethyl ester form of BCECF) that are cell membrane permeant, thus allowing intracellular concentrations of analytes to be measured when needed. Further evidence is provided by Applicant's disclosure which states on page 18 line 28 of the specification, "it is well known that specific dyes bind to cellular structures and allow imaging and anatomical/histological studies of intracellular structures". In addition Chick specifically teaches that a variety of modes of placing the reagents in communication with the analytes may be used (column 16 line 37).

One of ordinary skill in the art would have been motivated to use the acetoxymethyl ester form of BCECF in the method of Chick because Walt teaches that it is a suitable form of BCECF for use as a pH indicator, which is what Chick is using BCECF for (column 14 line 63). One of ordinary skill in the art would have had a reasonable expectation of success because Walt describes how the acetoxtmethyl ester form of BCECF passively enters the cell where, once inside the cell, the lipophilic blocking groups are cleaved by non-specific esterases resulting in an increase in fluorescent intensity.

One of ordinary skill in the art would have been motivated to use a calibration fluorophore (marker dye) such as coumarin in the method of Chick because Van Antwerp teach that this eliminates errors due to registration and variations of light transport through the skin (e. g, caused by different skin tones) (column 16 lines 24-30). One of ordinary skill in the art would have had a reasonable expectation of success because both Van Antwerp and Chick were measuring glucose levels with fluorescent dyes through the skin.

The application time for the sensor composition would clearly be a result effective variable since the penetration of the skin by the skin sensor would be required for the proper monitoring of the metabolites and analytes of an individual. The accuracy of the results of the method would indicate if the sensor composition had been applied for a sufficient amount of time. In addition, different formulations of sensor compositions would require different application times as well. According to 2144.05 of the MPEP, "Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Therefore, the selection of a specific application time clearly would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that the accuracy of the method and the formulation of the sensor composition would be dependent upon the application time.

Therefore, the combined teachings of Chick, Cote, Walt and Van Antwerp render obvious Applicant's invention as claimed.

Claims 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chick et al (US 6,040,194), Cote et al (US 6,485,703 B1), Walt et al (US 6,377,721) and Van Antwerp et al (US 6,319,540-from IDS) as applied to claims 19, 23-26, 28, 29, 30-36, 38, 39, 40-42 above, and further in view of Heller et al (US 5,972,199).

Claim 27 is drawn to the method of claim 19 as described above including lactate as the metabolite elected by Applicant.

Chick, Cote, Walt and Van Antwerp combined teach the method of Applicant as described above, but do not specifically include lactate as a metabolite to be measured.

Heller teaches that assay of biochemicals, such as glucose and lactate, is important in medicine, biotechnology and food processing (dairy and wine). Heller also teaches that monitoring of lactate in fluids of the human body is of relevance to diagnosis of trauma, of myocardial infarction, congestive heart failure, pulmonary edema, septicemia, hemorrhage, and others (column 1 lines 23-30).

Therefore, one of ordinary skill in the art would have been motivated to use the method of Chick to monitor levels of lactate in a patient because Heller teaches that monitoring of lactate in fluids of the human body is of relevance to diagnosis of trauma, of myocardial infarction, congestive heart failure, pulmonary edema, septicemia, hemorrhage, and others (column 1 lines 23-30). One of ordinary skill in the art would have had a reasonable expectation of success because Chick teaches that suitable analytes include inorganic or organic ions (column 5 line 15) and lactate is an ion that is found in bodily fluids.

Therefore, the combined teachings of Chick, Cote, Walt, Van Antwerp and Heller render obvious Applicant's invention as claimed.

Response to Arguments

Applicant's arguments with respect to claims 19, 23-36, 38-42, 54-56 have been considered but are moot in view of the new ground(s) of rejection – the addition of Van Antwerp for the newly added limitation of the marker dye.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura Schuberg whose telephone number is (571)272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura Schuberg

/JON P WEBER/

Supervisory Patent Examiner, Art Unit 1657